DOCKET NO: 285327US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
YUKIHIKO SAEKI, ET AL.	: EXAMINER: RAE, C. E.
SERIAL NO: 10/566,253	:
FILED: JANUARY 30, 2006	: GROUP ART UNIT: 1611
FOR: METHOD OF INHIBITING PRODUCTION OF OSTEOPONTIN	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an appeal of the Final Rejection dated May 1, 2008 of Claims 1-4 and 29-34. A Notice of Appeal was timely filed on June 27, 2008.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Kowa Co., Ltd., having an address at 6-29, Nishiki 3-chome, Naka-ku, Nagoya-shi, Aichi, Japan 460-8625.

II. RELATED APPEALS AND INTERFERENCES

Appellant, Appellant's legal representative and the assignee are aware of no appeals, interferences, or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 1-4 and 29-34 stand rejected and are herein appealed. Claims 5-28 have been canceled.

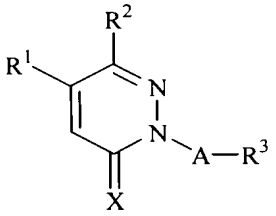
IV. STATUS OF THE AMENDMENTS

No amendment under 37 CFR 1.116 has been filed.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

A summary of the claimed subject matter, as claimed in independent Claims 1 and 29, are mapped out below, with reference to page and line numbers in the specification added in **[bold]** after each element.

Claim 1 is drawn to a method of inhibiting osteopontin (OPN) production, **[page 4, lines 13-14]** comprising administering to a subject in need thereof an effective amount of a pyridazine derivative represented by the following formula (I) **[page 4, lines 15-17]** or a salt thereof: **[page 6, line 7]**



(I) **[page 4, lines 18-19]**

wherein:

R^1 is a phenyl or pyridyl group which may be substituted by 1 to 3 substituents selected from halogen atoms and C_{1-6} alkoxy groups; **[page 4, line 21 to page 5, line 2]**

R^2 is a phenyl group which may be substituted at the 4-position thereof with a C_{1-6} alkoxy group or C_{1-6} alkoxythio group and may also be substituted at one or two other

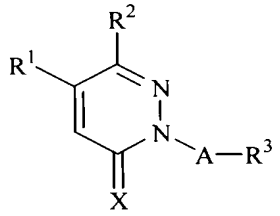
positions thereof a like number of substituents selected from halogen atoms, C_{1-6} alkoxy groups and C_{1-6} alkoxythio groups; **[page 5, lines 3-8]**

R^3 is a hydrogen atom; a C_{1-6} alkoxy group; a halogenated C_{1-6} alkyl group; a C_{3-6} cycloalkyl group; a phenyl, pyridyl or phenyloxy group, each of which may be substituted by 1 to 3 substituents selected from halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, carboxyl groups, C_{2-7} alkoxycarbonyl groups, nitro groups, amino groups, C_{1-6} alkylamino groups and C_{1-6} alkylthio groups; a substituted or unsubstituted piperidino, a substituted or unsubstituted piperidyl, a substituted or unsubstituted piperazino or a substituted or unsubstituted morpholino group; a substituted or unsubstituted aminocarbonyl group; a C_{2-7} alkylcarbonyl group; or a substituted or unsubstituted piperazinocarbonyl group; **[page 5, lines 9-20]**

A is a single bond, a C_{1-6} linear or branched alkylene group, or a C_{2-9} linear or branched alkenylene group; **[page 5, lines 21-23]** and

X is an oxygen atom or a sulfur atom, with a proviso that A is a single bond when R^3 is a halogenated C_{1-6} alkyl group. **[page 5, line 24 to page 6, line 1]**

Claim 29 is drawn to a therapeutic method of treating a disease resulting from enhanced OPN production, **[page 6, lines 20-22]**comprising administering to a subject in need thereof an effective amount of a pyridazine derivative represented by the following formula (I) **[page 4, lines 15-17]** or a salt thereof: **[page 6, line 7]**



(I) **[page 4, lines 18-19]**

wherein:

R^1 is a phenyl or pyridyl group which may be substituted by 1 to 3 substituents selected from halogen atoms and C_{1-6} alkoxy groups; **[page 4, line 21 to page 5, line 2]**

R^2 is a phenyl group which may be substituted at the 4-position thereof with a C_{1-6} alkoxy group or C_{1-6} alkoxythio group and may also be substituted at one or two other positions thereof a like number of substituents selected from halogen atoms, C_{1-6} alkoxy groups and C_{1-6} alkoxythio groups; **[page 5, lines 3-8]**

R^3 is a hydrogen atom; a C_{1-6} alkoxy group; a halogenated C_{1-6} alkyl group; a C_{3-6} cycloalkyl group; a phenyl, pyridyl or phenyloxy group, each of which may be substituted by 1 to 3 substituents selected from halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, carboxyl groups, C_{2-7} alkoxycarbonyl groups, nitro groups, amino groups, C_{1-6} alkylamino groups and C_{1-6} alkylthio groups; a substituted or unsubstituted piperidino, a substituted or unsubstituted piperidyl, a substituted or unsubstituted piperazino or a substituted or unsubstituted morpholino group; a substituted or unsubstituted aminocarbonyl group; a C_{2-7} alkylcarbonyl group; or a substituted or unsubstituted piperazinocarbonyl group; **[page 5, lines 9-20]**

A is a single bond, a C_{1-6} linear or branched alkylene group, or a C_{2-9} linear or branched alkenylene group; **[page 5, lines 21-23]** and

X is an oxygen atom or a sulfur atom, with a proviso that A is a single bond when R^3 is a halogenated C_{1-6} alkyl group. **[page 5, line 24 to page 6, line 1]**

VI. GROUNDS OF REJECTION

Ground (A)

Claims 1-4 and 29-34 stand rejected under 35 U.S.C. § 102(b) as anticipated by US 6,348,468 (Ohkuchi et al) in view of WO 00/63241 (Ashkar et al).[1]

Ground (B)

Claim 34 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Ohkuchi et al in view of Ashkar et al and McPhaden et al, *Plasma Osteopontin Levels in Multiple Myeloma*, Blood, J. American Society of Hematology, 1994; 84 (10, Suppl 1), page 172a, abstract 674 (McPhaden et al).

Ground (C)

Claim 1-4 and 29-32 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over Claims 7-9 of copending Application No. 11/574,319 (the copending application).

VII. ARGUMENT

Ground (A)

Claims 1-4 and 29-34 stand rejected under 35 U.S.C. § 102(b) as anticipated by Ohkuchi et al in view of Ashkar et al. That rejection is untenable and should not be sustained.

---

[1] That the new prior art, i.e., Ashkar et al, is not listed in the statement of the rejection is irrelevant; reliance thereon is all that is necessary. "Where a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of rejection." *In re Hoch*, 428 F.2d 1341, 166 USPQ 406, 407 n.3 (CCPA 1970). See also MPEP 706.02(j).

The presently-recited compounds are known, as described in the specification at paragraph [0016]. As described therein, the difference between the presently-claimed invention, and that disclosed in WO 99/25697, which is the WO equivalent of Ohkuchi et al, is that Applicants have discovered that the compounds of Ohkuchi et al have an osteopontin (OPN) production inhibiting effect, and are thus effective in treating certain diseases in which OPN production is implicated, such as those recited in present Claim 33.

Thus, the present invention is drawn to methods, which is either a method of inhibiting osteopontin (OPN) production, comprising administering to a subject in need thereof an effective amount of a pyridazine derivative represented by formula (I) or a salt thereof, as recited in Claim 1, or a therapeutic method of treating a disease resulting from enhanced OPN production, comprising administering to a subject in need thereof an effective amount of a pyridazine derivative represented by formula (I) or a salt thereof, as recited in Claim 29. Thus, the present method claims are drawn to treating a specific universe of subjects. Ohkuchi et al, on the other hand, is drawn to treating a universe of subjects in which interleukin-1β production is implicated. There is nothing in the prior art to suggest any nexus between interleukin-1β production and OPN production.

The Examiner relies on the disclosure in Ohkuchi et al of ischemic nephritis (column 13, line 20), which the Examiner finds is a kidney disease, which kidney disease is a member of the Markush group in Claim 33 herein.

In reply, Claim 33 is limited by the requirement that the members of the disease Markush group require that it result from enhanced OPN production. There are, of course, many kidney diseases. Ischemic nephritis has not been shown to result from enhanced OPN production.

In addition, the Examiner finds that inhibiting OPN production is an inherent characteristic of the presently-recited pyridazine compounds.

In reply, of course it is inherent, but its inherency is Applicants' discovery herein. Indeed, every property of a compound is inherent. But Applicants are not **claiming** the compounds. Ohkuchi et al does not disclose or suggest methods of using their compounds to treat diseases implicated by OPN production.

In the Final Rejection, page 6, the Examiner finds "[t]he recitation of the term 'administering to a subject in need thereof' does not in this case give life to the claimed underline [sic] mechanism of inhibiting osteopontin."

In reply, the Examiner's finding is inconsistent with applicable precedent. See *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003) (In considering the effect of the preamble in a claim directed to a method of treating or preventing pernicious anemia in humans by administering a certain vitamin preparation to "a human in need thereof," the court held that the claims' recitation of a patient or human "in need" gives life and meaning to the preamble's statement of purpose.)

In the Final Rejection, page 9, the Examiner for the first time relies on Ashkar et al to support a finding that "the treatment group taught by [Ohkuchi et al] overlaps with the targeted population encompassed by the instant claims as evidenced by the teaching of [Ashkar et al]."

In reply, Ashkar et al discloses OPN modulating agents, i.e., agents that stimulate or inhibit OPN activity. Ashkar et al's invention is based on a finding that OPN is a critical regulator of type-1 (cell-mediated) immunity and that this molecule includes a domain that promotes the production of type 1 cytokine IL-12 and a domain that inhibits the production of type 2 IL-10 (page 2, lines 22-25). The Examiner finds that Ashkar et al discloses that their OPN modulating agents can be used for treating cancer, AIDS, allergy, bacterial arthritis, granulomatous disorder, and glomerulonephritis.

In reply, that Ashkar et al may have discovered a group of OPN modulating agents that can be used to treat various diseases does not establish that the universe disclosed by Ohkuchi et al, i.e., subjects in need of inhibitory activity against interleukin-1β production, and the universe defined by the present claims, are the same or even overlap. Indeed, while various cytokines are described in Ashkar et al, there is not a single mention therein of interleukin-1β. Moreover, that the specific OPN modulator compounds of Ashkar et al are disclosed to have a utility against specific diseases in no way suggests that particular compounds disclosed as having inhibitory activity only against interleukin-1β production would be reasonably expected to have such activity against OPN production.

For all the above reasons, it is respectfully requested that this rejection be REVERSED.

Ground (B)

Claim 34 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Ohkuchi et al in view of Ashkar et al and McPhaden et al. That rejection is untenable and should not be sustained.

The deficiencies of the combination of Ohkuchi et al and Ashkar et al have been discussed above. McPhaden et al does not remedy these deficiencies. McPhaden et al simply discloses a connection between OPN production and multiple myeloma. However, Applicants do not profess to be the first to recognize this connection. Rather, Applicants have discovered that certain compounds inhibit the production of OPN, and thus are useful for treating multiple myeloma. Neither McPhaden et al, nor any other prior art, discloses any connection or nexus between inhibiting interleukin-1β production, as disclosed by Ohkuchi et al, and inhibiting OPN production.

In the Final Rejection, in response to the above arguments, the Examiner simply relies on the reasons found in the Office Action of September 12, 2007. Thus, there is no additional argument to rebut herein.

In the Final Rejection, page 7, as his response, the Examiner simply relies on the reasons found in the Office Action of September 12, 2007 and with regard to the rejection under Ground (A) above. Thus, there is no additional argument to rebut herein.

For all the above reasons, it is respectfully requested that this rejection be REVERSED.

Ground (C)

Claim 1-4 and 29-32 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over Claims 7-9 of the copending application. That rejection is untenable and should not be sustained.

The Examiner finds that the term "prevention ... of rheumatoid arthritis in a subject" reasonably encompasses treatment of subjects with or without arthritis e.g. multiple myeloma."

In reply, the Examiner has cited no evidence supporting any connection between prevention of rheumatoid arthritis and inhibiting of OPN production.

In the Final Rejection, in response to the above arguments, the Examiner simply relies on the reasons found in the Office Action of September 12, 2007. Thus, there is no additional argument to rebut herein.

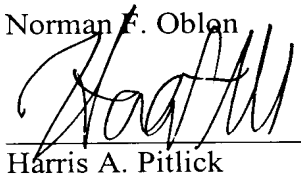
For all the above reasons, it is respectfully requested that this rejection be REVERSED.

VIII. CONCLUSION

For the above reasons, it is respectfully requested that all the rejections still pending in the Final Rejection be REVERSED.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Harris A. Pitlick
Registration No. 38,779

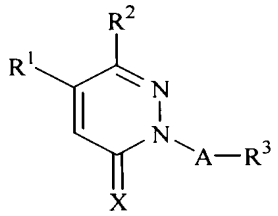
Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 03/06)

NFO:HAP\

CLAIMS APPENDIX

Claim 1: A method of inhibiting osteopontin (OPN) production, comprising administering to a subject in need thereof an effective amount of a pyridazine derivative represented by the following formula (I) or a salt thereof:



(I)

wherein:

R^1 is a phenyl or pyridyl group which may be substituted by 1 to 3 substituents selected from halogen atoms and C_{1-6} alkoxy groups;

R^2 is a phenyl group which may be substituted at the 4-position thereof with a C_{1-6} alkoxy group or C_{1-6} alkoxythio group and may also be substituted at one or two other positions thereof a like number of substituents selected from halogen atoms, C_{1-6} alkoxy groups and C_{1-6} alkoxythio groups;

R^3 is a hydrogen atom; a C_{1-6} alkoxy group; a halogenated C_{1-6} alkyl group; a C_{3-6} cycloalkyl group; a phenyl, pyridyl or phenyloxy group, each of which may be substituted by 1 to 3 substituents selected from halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, carboxyl groups, C_{2-7} alkoxycarbonyl groups, nitro groups, amino groups, C_{1-6} alkylamino groups and C_{1-6} alkylthio groups; a substituted or unsubstituted piperidino, a substituted or unsubstituted piperidyl, a substituted or unsubstituted piperazino or a substituted or unsubstituted morpholino group; a substituted or unsubstituted aminocarbonyl group; a C_{2-7} alkylcarbonyl group; or a substituted or unsubstituted piperazinocarbonyl group;

A is a single bond, a C_{1-6} linear or branched alkylene group, or a C_{2-9} linear or branched alkenylene group; and

X is an oxygen atom or a sulfur atom, with a proviso that A is a single bond when R^3 is a halogenated C_{1-6} alkyl group.

Claim 2: The method of claim 1, wherein in the formula (I),

R^1 is a phenyl or pyridyl group, each of which may be substituted at the 4-position thereof with a halogen atom selected from fluorine, chlorine and bromine, or a C_{1-6} alkoxy group;

R^2 is a phenyl group substituted at the 4-position thereof with a C_{1-6} alkoxy group or a C_{1-6} alkylthio group;

R^3 is a hydrogen atom, or a phenyl or pyridyl group, each of which may be substituted by halogen atom or atoms; and

A is a C_{1-3} alkylene group or C_{3-4} alkenylene group.

Claim 3: The method of claim 1, wherein in the formula (I),

R^1 is a phenyl or pyridyl group, each of which may be substituted at the 4-position thereof with a chlorine atom or a methoxy group;

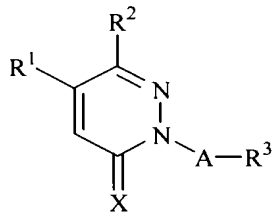
R^2 is a phenyl group substituted at the 4-position thereof with a methoxy group or a methylthio group;

R^3 is a hydrogen atom, phenyl group, 4-chlorophenyl group, 2-pyridyl group or 3-pyridyl group; and

A is a methylene group, ethylene group or 2-propenylene group.

Claim 4: The method of claim 1, wherein the active ingredient is 5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2-(2-pyridylmethyl)-2H-pyridazine-3-thione, 5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2-(3-pyridylmethyl)-2H-pyridazin-3-one, 5,6-bis(4-methoxyphenyl)-2-(4-chlorocinnamyl)-2H-pyridazin-3-one, 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one, 2-(4-chlorobenzyl)-6-(4-methoxyphenyl)-5-(4-pyridinyl)-2H-pyridazin-3-one, 5,6-bis(4-methoxyphenyl)-2-ethyl-2H-pyridazin-3-one, or a salt thereof.

Claim 29: A therapeutic method of treating a disease resulting from enhanced OPN production, comprising administering to a subject in need thereof an effective amount of a pyridazine derivative represented by the following formula (I) or a salt thereof:



(I)

wherein:

R^1 is a phenyl or pyridyl group which may be substituted by 1 to 3 substituents selected from halogen atoms and C_{1-6} alkoxy groups;

R^2 is a phenyl group which may be substituted at the 4-position thereof with a C_{1-6} alkoxy group or C_{1-6} alkoxythio group and may also be substituted at one or two other positions thereof a like number of substituents selected from halogen atoms, C_{1-6} alkoxy groups and C_{1-6} alkoxythio groups;

R^3 is a hydrogen atom; a C_{1-6} alkoxy group; a halogenated C_{1-6} alkyl group; a C_{3-6} cycloalkyl group; a phenyl, pyridyl or phenyloxy group, each of which may be substituted by

1 to 3 substituents selected from halogen atoms, C_{1-6} alkyl groups, C_{1-6} alkoxy groups, carboxyl groups, C_{2-7} alkoxycarbonyl groups, nitro groups, amino groups, C_{1-6} alkylamino groups and C_{1-6} alkylthio groups; a substituted or unsubstituted piperidino, a substituted or unsubstituted piperidyl, a substituted or unsubstituted piperazino or a substituted or unsubstituted morpholino group; a substituted or unsubstituted aminocarbonyl group; a C_{2-7} alkylcarbonyl group; or a substituted or unsubstituted piperazinocarbonyl group;

A is a single bond, a C_{1-6} linear or branched alkylene group, or a C_{2-9} linear or branched alkenylene group; and

X is an oxygen atom or a sulfur atom, with a proviso that A is a single bond when R^3 is a halogenated C_{1-6} alkyl group.

Claim 30: The method of claim 29, wherein in the formula (I),

R^1 is a phenyl or pyridyl group, each of which may be substituted at the 4-position thereof with a halogen atom selected from fluorine, chlorine and bromine, or a C_{1-6} alkoxy group;

R^2 is a phenyl group substituted at the 4-position thereof with a C_{1-6} alkoxy group or a C_{1-6} alkylthio group;

R^3 is a hydrogen atom, or a phenyl or pyridyl group, each of which may be substituted by halogen atom or atoms; and

A is a C_{1-3} alkylene group or C_{3-4} alkenylene group.

Claim 31: The method of claim 29, wherein in the formula (I),

R^1 is a phenyl or pyridyl group, each of which may be substituted at the 4-position thereof with a chlorine atom or a methoxy group;

R^2 is a phenyl group substituted at the 4-position thereof with a methoxy group or a methylthio group;

R^3 is a hydrogen atom, phenyl group, 4-chlorophenyl group, 2-pyridyl group or 3-pyridyl group; and

A is a methylene group, ethylene group or 2-propenylene group.

Claim 32: The method of claim 29, wherein the active ingredient is 5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2-(2-pyridylmethyl)-2H-pyridazine-3-thione, 5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2-(3-pyridylmethyl)-2H-pyridazin-3-one, 5,6-bis(4-methoxyphenyl)-2-(4-chlorocinnamyl)-2H-pyridazin-3-one, 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one, 2-(4-chlorobenzyl)-6-(4-methoxyphenyl)-5-(4-pyridinyl)-2H-pyridazin-3-one, 5,6-bis(4-methoxyphenyl)-2-ethyl-2H-pyridazin-3-one, or a salt thereof.

Claim 33: The method of claim 29, wherein said disease resulting from said enhanced OPN production is post-PTCA restenosis, a kidney disease, tuberculosis, sarcoidosis, cirrhosis, colorectal cancer, ovarian cancer, prostatic cancer, breast cancer, urinary calculus or myelomatous tumor.

Claim 34: The method of claim 29, wherein said disease resulting from said enhanced OPN production is multiple myeloma.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.